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(54) Title: COMPOSITIONS AND METHODS FOR HUMAN GASTROINTESTINAL HEALTH

(57) Abstract

A composition for promoting gastrointestinal health comprises an effective amount of a beneficial human intestinal microorganism and an effective amount of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins. Another composition for restoring and maintaining gastrointestinal health comprises 40-60 % by weight of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins and 40-60 % by weight of soluble dietary fiber selected from inulin, fructooligosaccharides, pectin, guar gum, and mixtures thereof. The immunoglobulin and fiber-containing composition can optionally contain one or more of a beneficial human intestinal microorganism, components of a non-immune natural defense system, an iron-sequestering molecule, and gluconic acid. Preferred beneficial human intestinal microorganisms include lactobacilli and bifidobacteria. The immunologically active immunoglobulins are preferably purified from bovine milk, milk products, or whey. Methods of use are also described.

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**COMPOSITIONS AND METHODS FOR HUMAN
GASTROINTESTINAL HEALTH**

Background of the Invention

This invention relates to compositions and methods for promoting gastrointestinal health. More particularly, the invention relates to a composition comprising (a) an immunoglobulin preparation containing immunoglobulins that are capable of binding and inactivating foreign antigens such as pathogenic bacteria, viruses, fungi, and protozoa that are detrimental to gastrointestinal health, and (b) living bacteria that are beneficial for gastrointestinal health. The invention also relates to another composition comprising (a) the immunoglobulin preparation containing immunologically-active immunoglobulins; (b) soluble dietary fiber that provides the advantages typically offered by dietary fibers with the additional advantages of not affecting blood glucose or insulin levels, being readily fermented by the intestinal microflora and promoting growth of certain beneficial intestinal microorganisms; and (c) optionally one or more of the following: living intestinal bacteria that are beneficial for gastrointestinal health, lactoperoxidase and/or thiocyanate for strengthening a natural non-immune defense system, lactoferrin for inhibiting detrimental iron-catalyzed processes and harmful microorganisms, and gluconic acid for inhibiting growth of harmful bacteria and stimulating immune function.

Since the time of Hippocrates and throughout the Middle Ages, large doses of whey were prescribed by alchemists for treating many ailments, primarily acute septic conditions. Although it was not then known the reason that whey was useful for treating such conditions, recent studies have shown that whey contains antibodies or immunoglobulins capable of providing passive immunity against various pathogens and their toxic by-products. Antibodies or immunoglobulins are

5 high molecular weight proteins produced in the bodies of
mature animals that enhance immunity to infection by
bacteria, viruses, fungi, protozoa, and the like.
Antibodies in human and bovine milk promote development
10 of a healthy gastrointestinal tract and provide
protection against infections by pathogenic
microorganisms. These antibodies interfere with the
process that allows such pathogenic microorganisms to
adhere to and colonize the intestinal lining. Studies
15 have shown that immunoglobulins from whey are
particularly effective against viruses (e.g.,
rotavirus), bacteria (e.g., *E. coli*, *Vibrio cholerae*,
Salmonella), fungi (e.g., *Candida*), and protozoa (e.g.,
Cryptosporidium).

20 Detectable levels of anti-rotavirus antibodies
(IgG₁) have been found in raw and pasteurized milk. R.H.
Yolken, *Antibody to Human Rotavirus in Cow's Milk*, 312
New Eng. J. Med. 605 (1985). The high temperatures used
in processing infant formula, however, destroy all
traces of naturally occurring IgG₁. Many infants develop
25 gastroenteritis around 6 months of age, about the time
they are weaned from breast milk and started on formula.

30 Since infants and young children are highly
susceptible to gastroenteritis, treatment of acute
diarrhea with concentrated immunoglobulins has been
investigated. In one study, infants hospitalized with
acute rotavirus gastroenteritis were treated with an
immunoglobulin concentrate derived from rotavirus-
immunized cows. H. Hilpert et al., *Use of Bovine Milk
Concentrate containing Antibody to Rotavirus to Treat
Rotavirus Gastroenteritis in Infants*, 156 J. Infect.
35 Dis. 158 (1987). These infants showed significantly
reduced duration of rotavirus excretion. Thus, bovine
milk immunoglobulins provided passive immunity against
rotavirus gastroenteritis in human infants.

40 A bovine milk immunoglobulin concentrate derived
from *E. coli*-immunized cows has also been shown to

5 inhibit colonization of enteropathogenic *E. coli* in affected
infants. C. Mietens et al., *Treatment of Infantile E. Coli Gastroenteritis with Specific Bovine Anti-E. Coli Milk Immunoglobulins*, Eur. J. Pediatrics (1979). Stool
10 samples showed a reduction in *E. coli* counts and the
duration of diarrhea was shortened, demonstrating that
this concentrate was effective in treating infantile
diarrhea.

15 Inflammation of the gastrointestinal mucosa and
diarrhea associated with Traveler's Diarrhea due to *E.*
coli infection have been prevented by treatment with an
immunoglobulin concentrate from bovine milk. C. Tacket
et al., *Protection by Milk Immunoglobulin Concentrate*
against Oral Challenge with Enterotoxigenic Escherichia
Coli, 318 N. Engl. J. Med. 1240 (1988).

20 Immunoglobulins from bovine colostrum have been
shown to be an effective treatment for diarrhea due to
a pathogenic protozoan, *Cryptosporidium*. S. Tzipori et
al., *Remission of Diarrhea Due to Cryptosporidiosis in*
an Immunodeficient Child Treated with Hyperimmune Bovine
25 *Colostrum*, 293 Br. Med. J. 1276 (1986). Immunodeficient
individuals, particularly those with acquired immune
deficiency syndrome (AIDS), are especially susceptible
to *Cryptosporidiosis*.

30 Certain bacteria have also been shown to be
beneficial to human gastrointestinal health. Bacteria
of the genus *Lactobacillus* have been used for several
hundred years for treating various illnesses.
Lactobacilli found in the human intestinal tract include
L. acidophilus, *L. casei*, *L. fermentum*, *L. salivaroae*,
35 *L. brevis*, *L. leichmannii*, *L. plantarum*, and *L.*
cellobiosus. In recent years, *L. acidophilus* has been
shown to be exceptionally useful in treating conditions
such as antibiotic-induced imbalances in the
gastrointestinal microflora, hypercholesterolemia,
40 vaginal infections, *E. coli* infection, oral
contraceptive failure, depressed immunity, cancerous

5 tumors, chronic granulomatous disease, and lactose
indigestion. A.G. Shauuss, *Method of Action, Clinical
Application, and Toxicity Data*, 3 J. Advancement Med.
163 (1990). *In vitro* studies have shown *L. acidophilus*
10 to have an inhibitory effect on the growth of pathogenic
bacteria such as *Campylobacter pylori*, *Staphylococcus
aureus*, *Pseudomonas aeruginosa*, and *Sarcina lutea*. K.M.
Shahani et al., *Natural Antibiotic Activity of
Lactobacillus Acidophilus and Bulgaricus*, 11 Cultured
Dairy Products J. 14 (1976).

15 The beneficial effect of *L. acidophilus* is further
illustrated by preliminary evidence that *L. acidophilus*
inhibits the toxic activities of bacteria in patients
with chronic kidney failure. M.L. Simenhoff et al.,
20 *Biomodulation of Uremic Pathophysiology in Man*, abstract
presented at Am. Soc. of Nephrology Meeting, Baltimore,
1992. Such patients often have toxic levels of amines
in their blood due to bacterial overgrowth in the small
bowel. Consumption of high levels of freeze dried
bacteria drastically reduced levels of these toxic
25 amines. These results demonstrate the ability of *L.
acidophilus* to exert a positive effect on the microflora
of the intestines.

30 It has also been shown that the activities of fecal
bacterial enzymes thought to play a role in conversion
of procarcinogens to carcinogens, such as beta-
glucuronidase, nitroreductase, and azoreductase, were
reduced 2- to 4-fold in subjects taking *L. acidophilus*
supplements. B.R. Goldin & L.S. Gorbach, *The Effect of
Milk and Lactobacillus Feeding on Human Intestinal
35 Bacterial Enzyme Activity*, 39 Amer. J. Clin. Nutr. 756
(1984). These results suggest that dietary
supplementation with *L. acidophilus* may reduce the risk
of developing colon cancer.

40 Bifidobacteria are also known to exert a beneficial
influence on human health. These bacteria exert
antimicrobial activity in the human intestine by

5 producing lactic acid and acetic acid as a result of carbohydrate metabolism. These acids lower the intestinal pH, thereby inhibiting overgrowth of gastrointestinal pathogens. Therapeutic applications of bifidobacteria are indicated for the management of
10 diarrhea and constipation, and the management of hepatic encephalopathy with hyperammonemia. Additional benefits include the production of B vitamins and breakdown of carcinogenic N-nitrosamines.

15 *Bifidobacterium adolescentis* is the predominant species of bacteria in humans after age two. This predominance suggests its exceptional stability and prolonged proliferation in the intestine. Nevertheless, for any preparation of living microorganisms to function as a commercial dietary supplement, in addition to being able to provide a beneficial effect must also exhibit good survival in storage, resistance to inactivation by bile, and survival through the gastrointestinal tract. Strain-to-strain or isolate-to-isolate variability can occur as to these traits, thus the selected properties
20 should be verified before commercializing any particular product containing such microorganisms.

25 Soluble fiber in the diet is also well known for its salutary effects on gastrointestinal health. Such effects include providing bulk to the stool, decreasing the pH of the gastrointestinal tract, producing volatile fatty acids, decreasing intestinal transit time, and beneficially influencing various blood parameters.
30 Dietary fiber has also been shown to have a beneficial effect on cholesterol and lipid metabolism that results in decreased serum cholesterol, triglycerides, and phospholipids and an improved (increased) HDL to LDL ratio. A study on laboratory animals showed that adding fiber to the diet decreases the incidence of bacterial translocation, i.e. crossing the intestinal barrier and
35 entering systemic circulation. C. Palacio et al.,
40 *Dietary Fiber: Physiologic Effects and Potential*

5 *Applications to Enteral Nutrition, in Clinical Nutrition: Enteral and Tube Feeding* (2d. ed., 1990). Nutritional and epidemiological studies have indicated that a general increase in the consumption of dietary fiber may play a role in preventing deleterious effects
10 of oxygen free radicals that have been accused of being involved in such processes as aging, inflammation, and some disease processes. R. Kohen et al., *Prevention of Oxidative Damage in the Rat Jejunal Mucosa by Pectin*, 69 Br. J. Nutrition 789 (1993).

15 While prior art formulas as dietary supplements containing soluble dietary fiber or immunoglobulins are known and are generally suitable for their limited purposes, they possess certain inherent deficiencies that detract from their overall utility in restoring and maintaining gastrointestinal health. For example, a dietary supplement containing soluble dietary fiber without concentrated immunoglobulins lacks means for binding and inactivating foreign antigens such as pathogenic bacteria, viruses, fungi, and protozoa that
20 can infect the gastrointestinal tract and are detrimental to the health thereof. Similarly, a dietary supplement containing concentrated immunoglobulins without soluble dietary fiber lacks means for providing bulk to the stool, decreasing the pH of the gastrointestinal tract, producing volatile fatty acids, decreasing intestinal transit time, beneficially influencing various blood parameters, beneficially influencing cholesterol and lipid metabolism, decreasing the incidence of bacterial translocation, preventing deleterious effects of oxygen free radicals, and favoring the growth of beneficial bacteria in the
25 gastrointestinal tract. Further, such prior art formulas fail to provide living intestinal bacteria that are beneficial for gastrointestinal health by providing an inhibitory effect on the growth of pathogenic bacteria, reducing levels of toxic amines, and lowering
30
35
40

5 the pH of the gastrointestinal tract. Further, prior art dietary supplements fail to provide components, such as lactoperoxidase and thiocyanate, that strengthen the body's natural non-immune defense system or LP-system. Moreover, these formulas do not contain inhibitors of
10 detrimental iron-catalyzed processes and stimulators of immune function.

In view of the foregoing, it will be appreciated that a composition for improving gastrointestinal health comprising living bacteria that exert a beneficial
15 effect on the gastrointestinal tract and an immunoglobulin preparation containing immunoglobulins that bind and inactivate pathogenic microorganisms in the gastrointestinal tract would be a significant advancement in the art. It will also be appreciated
20 that a composition for improving and maintaining gastrointestinal health comprising an immunoglobulin preparation containing immunoglobulins that bind and inactivate pathogenic microorganisms in the gastrointestinal tract and soluble dietary fiber that
25 provides the typical advantages of dietary fiber and additionally is low in calories, does not affect blood glucose or insulin levels, and favors the growth of beneficial bacteria in the gastrointestinal tract while at the same time inhibiting the growth of potentially
30 pathogenic or harmful microorganisms would be another significant advancement in the art.

Objects and Summary of the Invention

It is an object of the present invention to provide
35 a composition for use as a dietary supplement that benefits human gastrointestinal health when administered orally.

It is also an object of the invention to provide a composition for use as a dietary supplement that, when ingested, is effective for treating ailments due to
40

5 gastrointestinal pathogens such as bacteria, viruses, fungi, or protozoa.

10 It is another object of the invention to provide a composition for use as a dietary supplement that, when ingested, results in decreased serum cholesterol, triglycerides, and phospholipids and an increased HDL to LDL ratio.

15 It is still another object of the invention to provide a composition for use as a dietary supplement that aids in preventing deleterious effects of oxygen free radicals.

20 It is yet another object of the invention to provide a composition for use as a dietary supplement that bolsters the body's immune system and the natural non-immune system, the LP system.

25 It is a further object of the invention to provide a composition for use as a dietary supplement that inhibits detrimental iron-catalyzed processes in the body.

30 These and other objects can be accomplished by providing a composition for use as a dietary supplement for promoting gastrointestinal health comprising an effective amount of a beneficial human intestinal microorganism and an effective amount of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins. Such immunoglobulins can be obtained from any viable source, but are preferably obtained from bovine milk or a milk product. Most preferably, such immunoglobulins are purified from whey. The beneficial human intestinal microorganism is selected from the group consisting of lactobacilli and bifidobacteria. *Lactobacillus acidophilus* and *Bifidobacterium adolescentis* are preferred, and *L. acidophilus* strain NCFM is more preferred. The immunoglobulin composition can further comprise an inert carrier, such as a carbohydrate and/or a lipid.

5 A method of promoting gastrointestinal health comprises the step of orally administering an effective amount of the bacteria and immunoglobulin-containing composition described above. This method is also effective against bacteria, viruses, fungi, and protozoa
10 that cause diarrhea, constipation, and other forms of gastrointestinal distress.

15 An immunoglobulin and fiber-containing composition for use as a dietary supplement for restoring and maintaining gastrointestinal health comprises in percent by weight

(a) about 40 to about 60% of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins; and

20 (b) about 40 to about 60% of soluble dietary fiber, wherein the fiber is a member selected from the group consisting of inulin, fructo-oligosaccharides, pectin, guar gum, and mixtures thereof. The immunoglobulin and fiber-containing composition can optionally contain about 0 to about 20% by weight of a beneficial human intestinal microorganism selected from the group consisting of lactobacilli and bifidobacteria. Preferably, the beneficial human intestinal microorganism is present in an amount in the range of about 0.1 to about 20% by weight, and more preferably of
25 about 5 to about 10% by weight. The immunoglobulin and fiber-containing composition can also optionally contain one or more of the following ingredients:

5

The beneficial human intestinal microorganism is preferably selected from the group consisting of *Lactobacillus acidophilus*, *L. bulgaricus*, *L. casei*, *L. fermentum*, *L. salivaroes*, *L. brevis*, *L. leichmannii*, *L. plantarum*, *L. cellobiosus*, *Bifidobacterium adolescentis*, *B. infantis*, *B. longum*, *B. thermophilum*, and *B. bifidum*. More preferably, the beneficial human intestinal microorganism is selected from *L. acidophilus* and *B. adolescentis*. A preferred strain of *L. acidophilus* is strain NCFM.

The immunoglobulin composition can also include a carrier. A preferred carrier comprises at least one member selected from the group consisting of a carbohydrate and a lipid, wherein the carbohydrate is capable of being an energy source for a beneficial human intestinal microorganism and the lipid aids in reconstitution of the immunoglobulin composition. A preferred carbohydrate is maltodextrin, and a preferred lipid is lecithin. Preferably, the immunoglobulin composition is purified from a source selected from the group consisting of milk, milk products, and whey, with a bovine source also being preferred.

Ingredient	Ranges in Percent by Weight	
	Broad	Preferred
Lactoperoxidase	0-0.0300%	0.0001-0.0300%
Thiocyanate salt	0-0.0500%	0.0001-0.0500%
Lactoferrin	0-0.1000%	0.0001-0.1000%
Gluconic acid	0-10%	0.1-10%

5 A method of restoring and maintaining
gastrointestinal health comprises the step of orally
administering an effective amount of an immunoglobulin
and fiber-containing composition for promoting
gastrointestinal health comprising in percent by weight
10 (a) about 40 to about 60% of an immunoglobulin
composition comprising concentrated immunologically
active immunoglobulins; and
15 (b) about 40 to about 60% of soluble dietary
fiber, wherein the fiber is a member selected from the
group consisting of inulin, fructo-oligosaccharides,
pectin, guar gum, and mixtures thereof.

Brief Description of the Drawings

FIG. 1 shows growth curves for *Candida* (●) cultured
20 alone, and for a mixed culture of *Candida* (♦) and *L.
acidophilus* NCFM (▲).

FIG. 2 shows growth curves for *Candida* (●) cultured
25 alone, and for a mixed culture of *Candida* (♦) and *L.
acidophilus* NCFM (▲) also containing an immunoglobulin
composition according to the present invention.

FIG. 3 shows growth curves for *Candida* (●) cultured
30 alone, and for *Candida* (♦) cultured in the presence of
an equal amount of immunoglobulin composition as in FIG.
2.

FIG. 4 shows growth curves for *S. typhimurium* (●)
cultured alone, and for a mixed culture of *S.
typhimurium* (♦) and *L. acidophilus* NCFM (▲).

FIG. 5 shows growth curves for *S. typhimurium* (●)
cultured alone, and for a mixed culture of *S.
typhimurium* (♦) and *L. acidophilus* NCFM (▲) also
35 containing an immunoglobulin composition according to
the present invention.

Detailed Description of the Invention

40 Before the present composition and methods of use
are disclosed and described, it is to be understood that

5 this invention is not limited to the particular examples, process steps, and materials disclosed herein as such process steps and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing 10 particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

15 It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a composition containing "a microorganism" includes a mixture of two or more 20 microorganisms, reference to "an immunoglobulin" includes reference to two or more of such immunoglobulins, and reference to "a concentrate" includes reference to a mixture of two or more of such concentrates.

25 In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

30 As used herein, "immunoglobulin composition" means a composition comprising an effective amount of immunologically active immunoglobulins. Preferably, these are present as concentrated immunologically active immunoglobulins. One such immunoglobulin composition is sold under the trademark "PROBIOPLEX" by Metagenics, Inc. (San Clemente, California). PROBIOPLEX contains 35 (1) about 55-60 parts by weight of an immunoglobulin concentrate from bovine whey wherein at least about 7% by weight of the total solids in the concentrate is immunologically active immunoglobulins, (2) about 35-40 parts by weight of a mixture of carbohydrates including rice maltodextrin and lactose, and (3) about 5-10 parts 40 by weight of lipid including lecithin. Thus, at least

5 about 3.6% by weight of the total PROBIOPLEX composition comprises immunologically active immunoglobulins. The carbohydrates and lipids function as inert carriers for the immunoglobulins. The rice maltodextrin can function further as an energy source for beneficial
10 microorganisms with which the immunoglobulin composition can be mixed in accordance with the present invention. The lecithin aids in dispersion of the powder form of the immunoglobulin composition when reconstituted with water or other liquid. Although PROBIOPLEX contains
15 ingredients other than concentrated immunologically active immunoglobulins, these other ingredients are optional components of the invention. What is required is that the immunoglobulin composition contain an "effective amount" of immunologically active
20 immunoglobulins that are preferably present in concentrated form.

As used herein, "beneficial human intestinal microorganism" means an organism of microscopic size, such as a bacterium, that inhabits the human intestine and exerts a beneficial effect on the gastrointestinal health of an individual in which it resides. Preferred beneficial human intestinal microorganisms according to the present invention include bacteria of the genera *Lactobacillus* and *Bifidobacterium*. A more preferred lactobacillus is *L. acidophilus*, with *L. acidophilus* strain NCFM being most preferred, and a more preferred bifidobacterium is *B. adolescentis*. Other lactobacilli that are beneficial to gastrointestinal health include *L. bulgaricus*, *L. casei*, *L. fermentum*, *L. salivaroies*, *L. brevis*, *L. leichmannii*, *L. plantarum*, and *L. cellobiosus*. Other bifidobacteria that are beneficial to gastrointestinal health include *B. infantis*, *B. longum*, *B. thermophilum*, and *B. bifidum*.

As used herein, "effective amount" means an amount necessary to achieve a selected result. For example, an effective amount of an immunoglobulin and bacteria-

5 containing composition useful for reducing the titer of
a selected pathogenic microorganism in the
gastrointestinal tract would be an amount that achieves
the selected result of reducing the titer of the
microorganism. Such an amount can be readily determined
10 without undue experimentation by a person of ordinary
skill in the art. As another example, an effective
amount of an immunoglobulin and fiber-containing
composition useful for reducing the titer of a selected
pathogenic microorganism in the gastrointestinal tract
15 would be an amount that achieves the selected result of
reducing the titer of the microorganism. Such an amount
can also be readily determined without undue
experimentation by a person of ordinary skill in the
art.

20 As used herein, "thiocyanate salt" means a
nutritionally acceptable salt of the thiocyanate anion,
such as sodium thiocyanate, potassium thiocyanate,
ammonium thiocyanate, and mixtures thereof.

25 As reviewed above, immunoglobulin concentrates from
milk contain immunologically active immunoglobulins that
are capable of binding pathogenic microorganisms such as
bacteria, viruses, fungi, and protozoa. Such
immunoglobulin concentrates can be prepared from any
30 starting material containing sufficient concentrations
of immunologically active immunoglobulins, such as
milk, whey, blood, and the like. An economically viable
source of such immunoglobulins is the whey byproduct of
the cheese making process. It has been estimated that
35 approximately 85 million metric tons of whey are created
annually as a byproduct of cheese production worldwide.
About 34 million metric tons of whey are not
economically utilized, and thus are discarded. The whey
byproduct of cheese making, therefore, presents an
inexpensive and ready source of immunoglobulins.

40 Numerous techniques are known to exist for
producing dry concentrated protein extract from whey.

5 This protein extract is commonly referred to as whey
protein concentrate or "WPC." Such protein extraction
and concentration techniques have been primarily
concerned with preserving the food qualities of the WPC,
such as taste, flavor, and solubility. Although these
10 techniques are useful for producing food products, they
almost universally destroy or substantially reduce the
immunological activity of immunoglobulins in the
concentrate by exposing the raw milk, whey, or protein
concentrate to (1) excessive thermal (time and
15 temperature) conditions, (2) excessive bacterial
activity, or (3) excessive enzymes added in processing
or resulting from bacterial activity.

Methods have been developed for separating
immunologically active immunoglobulins from raw milk.
20 U.S. Patent Nos. 4,816,252 and 4,834,974 describe such
methods, which are illustrative of methods that can be
used for preparing an immunologically active
immunoglobulin concentrate according to the present
invention. Raw milk is first flash pasteurized to
25 control microbial activity in the milk without
significantly diminishing the immunological activity of
the immunoglobulins in the milk. Next, the milk is
exposed to an appropriate cheese starter culture, such
as a lactobacillus, at carefully controlled temperatures
30 and for limited times to achieve a selected degree of
curd formation without significantly affecting the
immunological activity of the immunoglobulins. The whey
is then separated from the cheese curd and transferred
to a clarifier or separator under carefully controlled
35 conditions to remove fat and casein particles. The
clarified whey is then subjected to ultrafiltration to
remove or substantially reduce the amounts of small
proteins, salts, and other non-protein materials in the
retained protein concentrate or retentate.
40 Ultrafiltration can be performed in stages to optimize
purification of the immunoglobulins. Optionally, other

5 concentration and purification steps, such as reverse
osmosis and ion exchange chromatography, can then be
used to further improve the purity and concentration of
the immunoglobulin concentrate while maintaining the
immunological activity thereof. The immunoglobulin
concentrate is then dried through conventional freeze-
drying or spray drying methods. The resulting dry
immunoglobulin concentrate can then be stored at room
temperature. At least about 7% of the total solids of
immunoglobulin concentrates prepared by these methods
15 comprise immunologically active immunoglobulins. When
ultrafiltration and ion exchange chromatography are both
used in the purification procedure, the proportion of
immunologically active immunoglobulins as a percentage
of total solids can be increased to at least about 50%.
20 Repeated ion exchange chromatography steps can further
increase the proportion of immunologically active
immunoglobulins as a percentage of total solids. U.S.
Patent Nos. 4,816,252 and 4,834,974 are hereby
incorporated herein by reference as illustrative of
25 methods for purifying immunologically active
immunoglobulin concentrate. The present invention is
not limited to these methods, however, and any method of
purifying and concentrating immunologically active
immunoglobulins from milk, whey, or another suitable
30 source is to be considered within the scope of the
invention as long as an effective amount of
immunologically active immunoglobulins is obtained in
the "immunoglobulin composition." Bovine milk and
bovine whey are preferred sources of immunoglobulins,
35 but other species of animal could also be used.

40 Certain bacteria have also been shown to be
beneficial to human gastrointestinal health, as briefly
reviewed above. The intestinal flora of the human gut
contains some 100×10^9 viable bacteria, representing 100
or more different species. The major bacteria can be
roughly divided into three groups: (a) lactic acid

5 bacteria, including lactobacilli, bifidobacteria, and streptococci; (b) anaerobic bacteria; and (c) aerobic bacteria.

Bacteria of the genus *Lactobacillus* have been used for several hundred years for treating various
10 illnesses. Bifidobacteria are also known to exert a beneficial influence on human health. Bifidobacteria constitute the predominant microorganisms in the fecal flora of week-old breast-fed infants, making up 85-99% of the bacterial population. Upon weaning or upon the
15 occurrence of perturbations such as an infection, vaccination, a sudden change in diet, and even the weather the balance of microorganisms in the gastrointestinal tract of these babies can be upset. Bifidobacteria can also be significantly reduced in
20 elderly people due to a reduction of secreted gastric juices. The bifidobacterial population in adults is much more stable, however changes in diet, administration of antibiotics, exposure to gamma radiation or X-rays, disease, stress, and other
25 disturbances can result in overgrowth of potentially pathogenic bacteria, decrease in beneficial bacteria (*lactobacilli* and *bifidobacteria*), and a resulting imbalance in the gastrointestinal flora. Hyperproliferation of harmful bacteria in the gut is associated with various forms of diarrhea,
30 susceptibility to systemic infections, constipation, vague and acute abdominal symptoms, fatigue, dyspepsia, and presence of carcinogenic metabolites. Reestablishment of a normal balance of gastrointestinal flora can be accelerated, and such normal balance maintained, with dietary administration of *lactobacilli*
35 and/or *bifidobacteria*.

Lactobacilli and bifidobacteria produce organic acids that reduce intestinal pH and thereby inhibit the growth of acid-sensitive undesirable bacteria.
40 Lactobacilli produce lactic acid, hydrogen peroxide, and

5 possibly acetic and benzoic acids. Bifidobacteria produce short chain fatty acids (SCFA) such as acetic, propionic, and butyric acids, as well as lactic and formic acids. The most plentiful short chain fatty acid produced by bifidobacteria is acetic acid, which has a
10 wide range of antimicrobial activities against yeasts, molds, and other bacteria. Additionally, short chain fatty acids support normal gastrointestinal function by increasing colonic blood flow, stimulating pancreatic enzyme secretion, promoting sodium and water absorption,
15 and potentiating intestinal mucosal growth.
Bifidobacteria are also known to deconjugate bile salts to free bile acids, which are more inhibitory to susceptible bacteria than are the conjugated forms.
Further, lactobacilli and bifidobacteria are able to
20 produce other antimicrobial substances, such as bacteriocins, that inhibit the growth and proliferation of harmful bacteria in the gut.

The advantages of soluble dietary fiber have also been briefly reviewed above. Inulin is one such fiber that is composed of a mixture of oligomers and polymers of fructose. Inulin is a storage carbohydrate found in many plants including onion, asparagus, artichoke, and many cereals. Chicory root and Jerusalem artichoke each contain about 70% by weight of inulin. Inulin has been
25 an important food in Europe for many years and is currently being used as a source of dietary fiber, for replacing fat in the diet, and for promoting growth of beneficial bacteria in the intestine. In the U.S., inulin is added to all types of noodles. It has a moderately sweet taste, is highly soluble, and is a frequent replacement for sugar in many foods.
30 Medically, inulin is the substance of choice to study renal clearance and impaired kidney function.
35

Fructo-oligosaccharides (FOS) are another type of
40 soluble dietary fiber. FOS is widely distributed in nature and is found in honey, beer, onion, asparagus,

5 Chinese chive, banana, maple sugar, oats, and Jerusalem artichoke.

Upon ingestion, both inulin and FOS are hydrolyzed to a negligible extent as they pass through the mouth, stomach, and small intestine. In the large intestine, 10 they are readily fermented by the intestinal microflora. These carbohydrates are metabolized by the bacteria into short chain fatty acids, mainly acetic, propionic, butyric, and lactic acids. As a consequence of this 15 fermentation, a considerable amount of bacterial mass is produced, which increases stool wet weight. The short chain fatty acids are absorbed by the large intestine and are further metabolized in the liver. This allows the body to recover some energy from inulin and FOS, although the efficiency of energy conversion is markedly 20 lower than with other carbohydrates. This phenomenon underlies the low calorie content of fructans and dietary fibers.

Inulin and FOS are used as a source of energy in the intestinal tract mainly by bacteria in the genus 25 *Bifidobacterium*. H. Hidaka et al., *Effects of Fructooligosaccharides on Intestinal Flora and Human Health*, 5 *Bifidobacteria Microflora* 37-50 (1986). When inulin and FOS are administered in the diet, the bifidobacteria increase significantly, becoming the predominant bacteria in the intestinal population, and the clostridia, which are a measure of potentially 30 pathogenic microorganisms, are significantly reduced. As will be discussed in more detail below, bifidobacteria are human intestinal bacteria that provide beneficial effects on gastrointestinal health. Other important groups of bacteria in the mixed 35 population in the intestines, such as *Fusobacterium*, *Lactobacillus*, and aerobic bacteria, are not significantly affected by the administration of inulin and FOS. H. Hidaka et al., *Effects of*

5 *Fructooligosaccharides on Intestinal Flora and Human Health*, 5 Bifidobacteria Microflora 37-50 (1986).

10 It has been shown, A. Hata, *The Influence of Neosugar on the Lipid Metabolism of Experimental Animals*, Proc. 1st Neosugar Res. Conference, Tokyo (1982), that fructo-oligosaccharides (FOS) in the diet of experimental animals cause reduction of blood sugar, serum cholesterol, triglycerides, and phospholipids; significant improvement in the HDL/LDL ratio; an increase in free fatty acids; and significant decreases in total cholesterol in lipedemia cases.

15 It has also been shown, H. Hadaka et al., *Effects of Fructooligosaccharides on Intestinal Flora and Human Health*, 5 Bifidobacteria Microflora 37-50 (1986), that administration of fructo-oligosaccharides (FOS) enhances 20 growth of the bifidobacteria population in the intestine, suppresses production of putrefactive factors, improves blood lipid levels in hyperlipidemia patients, and provides relief from constipation.

25 Therefore, at least the following positive effects are obtained by addition of inulin and/or fructo-oligosaccharides (FOS) to a composition for use as a dietary supplement according to the present invention: reduction of intestinal disorders, enhancement of a balanced intestinal microflora, and remediation of 30 constipation.

35 Other preferred dietary fibers according to the present invention include pectin and guar gum. Pectin is a highly water soluble, noncellulosic polysaccharide fiber extracted from the primary cell walls of plants. Rich sources of pectin include lemon and orange rinds, which contain about 30% by weight of this polysaccharide. Pectin occurs naturally as a partial methyl ester of α -(1 \rightarrow 4) linked D-polygalacturonate sequences interrupted with (1 \rightarrow 2)-L-rhamnose residues. 40 Pectins are used as gelling and thickening agents in food technology and as an antidiarrheal in veterinary

5 medicine. Guar gum is produced from the ground
endosperms of *Cyamopsis tetragonolobus*, a legume
cultivated in India as a livestock feed. The water
soluble fraction, which comprises about 85% of guar gum
and is known as guaran, consists of linear chains of
10 (1 \rightarrow 4)- β -D-mannopyranosyl units with α -D-galactopyranosyl
units attached by (1 \rightarrow 6) linkages. The ratio of D-
galactose to D-mannose is 1:2. Guar gum has 5 to 8
times the thickening power of starch and, thus, is used
15 as a thickener in foods, as a binder and disintegrating
agent in tablet formulations, and in pharmaceuticals and
cosmetics.

Pectin and guar gum have several beneficial effects
on the gastrointestinal tract, such as maintaining the
morphology of intestinal villi, increasing lipase
20 activity in the small bowel, delaying gastric emptying
time, increasing intestinal transit time, and promoting
increased fecal production of short chain fatty acids.
It is believed that pectin and guar gum in the diet
lower blood glucose and serum cholesterol levels, B.
25 Flourie et al., *The Effect of Pectin on Jejunal Glucose
Absorption and Unstirred Layer Thickness in Normal Man*,
25 Gut 1936 (1984). Also, dietary fiber supplementation
with pectin or guar gum has also been found to
significantly suppress the incidence of colon cancer.
30 G. Arbman, *Cereal Fiber, Calcium and Colorectal Cancer*,
69 Cancer 2042 (1992). Studies with whole apples show
that fiber (pectin) in the fruit reduces the insulin
response to the sugar in the fruit and prevents
"rebound" hypoglycemia. D. Jenkins et al., *Dietary
35 Fiber, Fiber Analogues and Glucose Tolerance, Importance
of Viscosity*, 1 Br. Med. J. 1392 (1978). Further,
pectin and guar gum are readily degraded by bacterial
fermentation in the colon, probably because of their
high water solubility.

40 Moreover, pectin and guar gum are also thought to
prevent oxidative damage in the gastrointestinal tract.

5 Oxygen free radicals are involved in many deleterious processes including aging, inflammation, and some disease processes. The gastrointestinal mucosa is exposed to oxidants produced within the lumen and in the epithelial cells. Potential sources of luminal oxidants include ingested food, catalase-negative bacteria, and cigarette smoke and other pollutants. The production of reactive free radicals during metabolism of dietary fat can explain some the biological damage such as loss of membrane function, inactivation of membrane-bound enzymes, and inactivation of essential molecules located 10 inside the cell. Other tests have shown that a large amount of fat in the diet can be a presumptive carcinogen. H. Hidaka et al., *Effects of Fructooligosaccharides on Intestinal Flora and Human Health*, 5 Bifidobacteria Microflora 37-50 (1986). Apart 15 from these carcinogenic changes, still other injuries associated with free radicals include ulcerative diseases, inflammation, and ischemic bowel disease. Pectin and guar gum prevent oxidative damage in various ways. They directly scavenge intestinal oxidants. Further, pectin can act as a chelating agent of loosely bound transition metals in the lumen. Moreover, pectin also reacts directly to prevent spontaneous dismutation 20 of superoxide radicals and thus prevents the formation of hydrogen peroxide.

In human and animal tissues, peroxidases form part of a natural non-immune defense system and also play a role in protecting against microbial invasion of mucous membranes. Peroxidases occur in various exocrine gland 35 secretions including salivary, lachrymal, bronchial, nasal, and intestinal secretions and in milk. Milk peroxidases, known as lactoperoxidases (LP) are the predominant enzymes in bovine milk. LP has no intrinsic antibacterial activity, however, together with hydrogen peroxide and thiocyanate anion it forms a potent natural 40 antibacterial system, the so-called lactoperoxidase or

5 LP system (for review see B. Reiter, *Bacterial Inhibitors in Milk and Other Secretions with Special Reference to the Complement, Transferrin and Lactoperoxidase/Thiocyanate/Hydrogen Peroxide Systems, in Inhibition and Inactivation of Vegetative Microbes*,
10 31-60 (1976); B. Reiter & J.-P. Perraudin, *Lactoperoxidase: Biological Functions, in 1 Peroxidases in Chemistry and Biology* 143-180 (1991). The antibacterial effect of the LP system is mediated by the generation of short-lived oxidation products of
15 thiocyanate anion (SCN), mainly the hypothiocyanate ion (OSCN). LP is a highly active enzyme, and very low concentrations are sufficient to establish an effective system. A wide range of bacterial species is affected by the LP system. Gram-negative bacteria generally are killed or their growth inhibited. Gram-positive bacteria usually are more resistant, however, and in general only their growth is inhibited. The LP system can also affect certain viruses, yeasts, and molds.

20 The thiocyanate anion is widely distributed in animal and human tissues, body-fluids, and secretions. It is found in the mammary, salivary, and thyroid glands, in the stomach and kidneys, in synovial, cerebral, and spinal fluid, and in lymph and plasma. The major dietary sources of thiocyanate ion are vegetables such as cabbage, cauliflower, and turnip, which are rich in glucosinolates that yield thiocyanate ion upon hydrolysis.

25 The activity of the LP system arises from an LP-catalyzed reaction in which hydrogen peroxide oxidizes thiocyanate ion (SCN) to form the hypothiocyanate ion (OSCN). The hypothiocyanate ion then oxidizes sulphydryl groups in vital metabolic enzymes and other proteins of the microorganisms. The mechanisms of antimicrobial activity of the LP system result in damage to bacterial membranes and inhibition of essential transport mechanisms, such as those involving glucose

5 and amino acids, and inhibition of synthesis of nucleic acids and proteins, including vital metabolic enzymes such as those involved in glycolysis.

10 Microorganisms inhibited by the LP system include a number of Gram-positive bacteria, including species of *Staphylococcus* and *Streptococcus*, and some Gram-negative species, e.g., *E. coli*, *Salmonella*, *Pseudomonas*. Some lactic acid bacteria, e.g. *lactobacilli* and *bifidobacteria*, are unaffected by the LP system because they contain a "reversal enzyme" called NAD(P)-OSCN-oxidase reductase, which prevents the antimicrobial activity of the LP system.

20 Lactoperoxidase is a highly active enzyme, and very low concentrations, along with low concentrations of hydrogen peroxide and thiocyanate ion, are sufficient to obtain an effective system. Hydrogen peroxide is known to be produced in many species of *lactobacilli*, and thiocyanate ion is widely distributed in animal and human tissues, body fluids, and secretions.

25 Advantages of the LP system include a greater antimicrobial efficacy and a wider spectrum of activity than existing preservatives. Also, the active antimicrobial agents of the LP system (OSCN and HOSCN) disappear from food after processing, thus providing a safe, long-lasting food preservative without the presence of the active preservative agents. Further, the LP system acts in synergy with other preservatives, thus increasing the efficacy of such other preservatives. Moreover, the LP system has a very low level of toxicity.

35 Lactoferrin is an iron-binding protein present in milk. For example, bovine milk contains about 200 mg/l of lactoferrin, and human milk and colostrum contain about 2-4 g/l and 6-8 g/l of lactoferrin, respectively. The affinity of lactoferrin for iron is very high, e.g. about 300 times that of the iron-transporting protein, transferrin, in blood plasma. A lactoferrin molecule

5 binds one ferric ion (Fe^{3+}) by means of a bicarbonate-dependent reaction.

The high affinity for iron enables the use of lactoferrin for inhibiting iron-catalyzed processes, such as generation of free hydroxyl radicals, lipid 10 peroxidation, and growth of microorganisms. Most microorganisms need iron for growth. Lactoferrin is able to inhibit the growth of such microorganisms by depriving them of iron. Lactoferrin is bacteriostatic 15 to a wide range of microorganisms, including Gram-negative bacteria with a high iron requirement and some Gram-positive bacteria. Lactic acid bacteria, such as lactobacilli and bifidobacteria, have a low iron requirement and, in general, are not affected by lactoferrin. Although lactoferrin is primarily 20 bacteriostatic, heat-treated lactoferrin is bactericidal. Heat-treated lactoferrin is easily obtained by heating lactoferrin at acidic pH.

Lactoferrin has been demonstrated in *in vitro* and 25 *in vivo* tests to be effective against a variety of microorganisms, including *E. coli*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Candida albicans*, while at the same time promoting the growth of bifidobacteria. Lactoferrin retains iron at low pH and can pass through the acid environment of the stomach and 30 enter the intestine unaltered.

As described above, various indigestible saccharides, such as FOS, have been developed for 35 promoting the growth of bifidobacteria. Another substance that promotes the growth of bifidobacteria is gluconic acid and its salts (gluconates). It has been shown in *in vitro* fermentation tests that gluconate is utilized selectively by bifidobacteria as an energy source. H. Sato et al., *Antioxidant Activity of Synovial Fluid, Hyaluronic Acid, and Two Subcomponents of Hyaluronic Acid*, 31 *Arthritis & Rheumatism* (1988). In addition to promoting the growth of bifidobacteria,

5 gluconic acid, like other organic acids, also suppresses
the growth of certain harmful bacteria, such as
Clostridium perfringens. Test results have further
shown that ingested gluconic acid and gluconates are not
absorbed in the small intestine, but instead are able to
10 reach the large intestine where they can be utilized as
an energy source by bifidobacteria. Sato et al.,
Antioxidant Activity of Synovial Fluid, Hyaluronic Acid,
and Two Subcomponents of Hyaluronic Acid, 31 Arthritis
& Rheumatism (1988).

15

Bacteria and Immunoglobulin-Containing Composition

A bacteria and immunoglobulin-containing composition according to the present invention comprises a mixture of an immunoglobulin composition and a beneficial human intestinal bacterium, such as a lactobacillus or a bifidobacterium or mixtures thereof. The composition is made by mixing dry immunologically active immunoglobulins with dry beneficial human intestinal bacteria. The bacteria are prepared, for example, by culturing in a rich medium such as LB, J. Miller, Experiments in Molecular Genetics, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1972), until the late log phase of growth is reached. The bacteria are then concentrated and lyophilized according to standard methods. The dry immunoglobulins and dry bacteria are then mixed in selected proportions. Just prior to consumption, the dry composition is reconstituted with water, juice, or the like to result in a smooth liquid composition that can be consumed orally.

It has been found that oral administration of such a bacteria and immunoglobulin-containing composition has a beneficial effect on gastrointestinal health. Although immunoglobulin compositions containing immunologically active immunoglobulins and beneficial bacteria such as lactobacilli and bifidobacteria each

5 have some effect on diminishing the growth of pathogenic microorganisms in the gastrointestinal tract, it has been surprising to discover that a composition containing a mixture of the immunoglobulin composition and beneficial bacteria has a synergistic effect in
10 causing death of the pathogenic microorganisms and in restoring gastrointestinal health. Regular consumption of the bacteria and immunoglobulin-containing composition has the effect of maintaining good gastrointestinal health. The bacteria and
15 immunoglobulin-containing composition contains an effective amount of each of the bacterial and immunoglobulin components, and preferably contains weight ratios of bacteria to immunologically active immunoglobulins in the range of about 20:1 to about
20 1:20. More preferably, the weight ratios of bacteria to immunologically active immunoglobulins are in the range of about 1:5 to about 10:1.

The effects of exposing pathogenic microorganisms to bacteria and immunoglobulin-containing compositions according to the present invention are illustrated in the following examples. These examples are merely illustrative and are not intended to delimit the scope of the invention.

30

EXAMPLE 1

In vitro cultures of *Candida albicans* were prepared by subculturing from a stock culture in a rich liquid medium. Cultures were incubated at 37°C, and cells were counted by dilution and plating on plate count agar.
35 FIG. 1 shows cell viability in cultures containing *C. albicans* alone (●) and cultures containing both *C. albicans* (♦) plus *L. acidophilus* strain NCFM (▲). During the course of this study, the *C. albicans* multiplied at the same rate regardless of the presence or absence of the *L. acidophilus* NCFM. The number of 40 viable *L. acidophilus* NCFM cells, however, was

5 diminished by a factor of about 20 in the presence of *C. albicans* cells.

EXAMPLE 2

10 FIG. 2 shows the cell viability in cultures containing *C. albicans* alone (●) and cultures containing both *C. albicans* (♦) and *L. acidophilus* strain NCFM (▲) as in Example 1, with the exception that the immunoglobulin composition containing immunologically active immunoglobulins was added to the mixed cultures of *C. albicans* plus *L. acidophilus* strain NCFM in a weight ratio of 1 part of *L. acidophilus* strain NCFM to 5 parts of immunoglobulin composition. Two predominant differences occurred in this example compared to Example 1. First, the viability of *L. acidophilus* strain NCFM was enhanced by a factor of about 4 to 5 in the presence of the immunoglobulin composition as compared to cultures in which the immunoglobulin composition was absent. Second, the viability of *C. albicans* was greatly reduced after about 20 hours of co-culturing 15 with *L. acidophilus* strain NCFM in the presence of the immunoglobulin composition. In other experiments, it has been found that the immunoglobulin composition by itself did not affect the viability of *C. albicans* (FIG. 3). Thus, although neither *L. acidophilus* strain NCFM nor the immunoglobulin composition alone affected the growth and viability of *C. albicans* *in vitro*, the mixture of *L. acidophilus* strain NCFM and the immunoglobulin composition caused a rapid decline in the 20 viability of *C. albicans*. Further, the growth and viability of *L. acidophilus* strain NCFM was enhanced in co-culture with *C. albicans* in the presence of the immunoglobulin composition as compared to when the immunoglobulin composition was absent. These results were unforeseen, i.e. that the combination of beneficial 25 bacteria and immunoglobulins would yield a better result than the additive effects of the bacteria and the 30 35 40

5 immunoglobulins, and that the immunoglobulins would
improve the viability of the bacteria in co-culture with
another microorganism. Further, these results were
considered predictive of what would occur *in vivo* since
lactobacilli are known to survive in the
10 gastrointestinal tract and immunoglobulins have been
shown to provide passive immunity to certain pathogens
upon oral administration.

EXAMPLE 3

15 *In vitro* cultures of *Salmonella typhimurium* were
prepared by subculturing from a stock culture in a rich
liquid medium, J. Miller, Experiments in Molecular
Genetics, Cold Spring Harbor Laboratory, Cold Spring
Harbor, N.Y. (1972). Cultures were incubated at 37°C,
20 and cells were counted by dilution and plating on plate
count agar.

25 FIG. 4 shows growth curves for cultures containing
S. typhimurium alone and cultures containing *S.*
typhimurium plus *L. acidophilus*. Cultures containing *S.*
typhimurium (●) alone reached stationary phase with a
maximum number of viable cells after about 10 hours of
growth. Cultures containing a mixture of *S. typhimurium*
and *L. acidophilus* strain NCFM also resulted in maximum
numbers of viable cells of *S. typhimurium* (♦) at about
30 10 hours, although the number of viable cells was
diminished about 100-fold compared to *S. typhimurium*
cultured alone. The cell viability of *L. acidophilus*
strain NCFM (▲) appeared to unaffected by the presence
of *S. typhimurium*.

35

EXAMPLE 4

40 FIG. 5 shows the cell viability in cultures
containing *S. typhimurium* alone (●) and cultures
containing both *S. typhimurium* (♦) plus *L. acidophilus*
strain NCFM (▲) as in Example 4 with the exception that
the immunoglobulin composition containing

30

5 immunologically active immunoglobulins was added to the
mixed cultures of *Candida* plus *L. acidophilus* strain
NCFM in a weight ratio of 1 part of *L. acidophilus*
strain NCFM to 5 parts of immunoglobulin composition.
These results show that when *S. typhimurium* is cultured
10 in the presence of both *L. acidophilus*
strain NCFM and whey immunoglobulins, the *S. typhimurium*
failed to produce as many viable cells after 10 hours of
growth, and the viability of *S. typhimurium* was greatly
reduced through the duration of the experiment as
15 compared to growth in co-culture with *L. acidophilus*
strain NCFM without the immunoglobulins. Therefore, the
mixture of *L. acidophilus* strain NCFM and the
immunoglobulin composition greatly decreased the
viability of *S. typhimurium* *in vitro* compared to growth
20 in the presence of either the immunoglobulin composition
or *L. acidophilus* strain NCFM alone. There appears to
be an unexpected synergistic effect in diminishing *S.*
typhimurium viability by combining the immunoglobulin
composition and *L. acidophilus*.

25

EXAMPLE 5

A strain of *E. coli* isolated from human intestine
was cultured alone, in the presence of *L. acidophilus*
strain NCFM, and in the presence of both *L. acidophilus*
30 strain NCFM and the immunoglobulin composition in a
weight ratio of about 1:10. The results were similar to
those of Examples 4 and 5, wherein the viability of the
E. coli was greatly diminished in the presence of both
L. acidophilus strain NCFM and the immunoglobulin
35 composition as compared to in the presence of either
alone.

The composition of the present invention can be
used for maintaining gastrointestinal health as well as
for treating diarrhea, constipation, and other types of
40 gastrointestinal distress due to infection with
pathogenic microorganisms such as *E. coli*, *Salmonella*,

5 Candida, rotavirus, and Cryptosporidium by orally
administering an effective amount of the composition.
The effective amount will vary depending on the size and
age of the individual, whether the selected effect is to
maintain gastrointestinal health or to restore
10 gastrointestinal health from distress due to infection
with a pathogenic microorganism, the particular
pathogenic microorganism involved, and the like. A
person skilled in the art can routinely determine such
an effective amount. The dry ingredients of the
15 composition are stirred into water or juice, and the
resulting suspension is taken by mouth. Preferably,
dosage is in the range of about 1 to about 100 mg/kg of
body weight. More preferably, dosage is in the range of
about 5 to about 50 mg/kg of body weight. Doses of the
20 bacteria and immunoglobulin-containing composition can
be divided, wherein two or more administrations of
divided doses are used to deliver a complete dose.
Multiple doses can also be administered, but it is
recommended that daily consumption be limited to 1 to 3
25 doses.

EXAMPLE 6

An adult afflicted with diarrhea due to infection
with *Salmonella* was treated with a composition according
30 to the present invention containing about 5 parts by weight
of *L. acidophilus* NCFM and about 1 part by weight of an
immunoglobulin composition comprising concentrated
immunologically active immunoglobulins purified from
bovine whey. Doses of about 10 mg/kg of body weight
35 were taken by mouth 3 times daily by stirring into water
or juice and drinking the resulting suspension.
Symptoms began to subside within 24 hours and had
completely disappeared within 3 days.

5

EXAMPLE 7

A small child afflicted with diarrhea due to rotavirus infection was treated with a composition according the present invention containing 5 parts by weight of *B. adolescentis* and 1 part by weight of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins purified from bovine whey. A dose of about 20 mg/kg of body weight was taken by mouth once daily by stirring into water or juice and drinking the resulting suspension. Symptoms began to subside within 24 hours and had completely disappeared within 3 days.

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EXAMPLE 8

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An adult afflicted with diarrhea due to infection with *Cryptosporidium* is treated with a composition according the present invention containing a weight ratio of about 5:1 of *L. acidophilus* NCFM to concentrated immunologically active immunoglobulins purified from bovine whey. Doses of about 10 mg/kg of body weight are taken by mouth 3 times daily by stirring into water or juice and drinking the resulting suspension. Good gastrointestinal health is restored.

EXAMPLE 9

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35

An adult afflicted with diarrhea due to infection with *Candida* is treated with a composition according to the present invention containing a weight ratio of about 1:5 of *B. adolescentis* to concentrated immunologically active immunoglobulins purified from bovine whey. Doses of about 5 mg/kg of body weight are taken by mouth 3 times daily by stirring into water or juice and drinking the resulting suspension. Good gastrointestinal health is restored.

40

5

EXAMPLE 10

An adult who averages 10 episodes of gastrointestinal distress per year takes a daily dose of about 50 mg/kg of body weight of a 5:1 weight ratio of the bacteria and immunoglobulin-containing composition according to the present invention with water or juice.

In the ensuing year, only 1 episode of gastrointestinal distress is experienced. This example shows that not only can the bacteria and immunoglobulin-containing composition of the present invention be used for treating acute cases of gastrointestinal distress, but is also effective as a dietary supplement in maintaining good gastrointestinal health.

10

EXAMPLE 11

15

Various formulations of the bacteria and immunoglobulin-containing composition are tested in treating acute episodes of gastrointestinal distress, as summarized in Table 1.

5

Table 1			
Bacteria ^a	Immunoglobulins ^a	Condition	Result ^b
10	0.2	1	diarrhea
	0.2	25	diarrhea
	5	1	diarrhea
	5	25	diarrhea
	0.1	100	diarrhea
	100	0.1	diarrhea
15	0.5	2.5	diarrhea
	0.5	10	diarrhea
	2	2.5	diarrhea
	2	10	diarrhea
	1	4	constipation
	4	1	constipation
20	1	3	gas/cramps
	3	1	gas/cramps

a Parts by weight.

b Symbols represent a relative scale for
restoring gastrointestinal health: +++,
excellent; ++, very good; +, good; -, poor.

25

Immunoglobulin and Fiber-Containing Composition

In accordance with a preferred embodiment of the present invention, there is provided an immunoglobulin and fiber-containing composition for use as a dietary supplement. The formulation preferably includes a mixture of an immunoglobulin composition and a soluble dietary fiber selected from the group consisting of inulin, fructo-oligosaccharide, pectin, guar gum, and mixtures thereof in optimal ratios to restore and maintain good gastrointestinal health.

In its most fundamental form, the immunoglobulin and fiber-containing formulations of the present invention include a mixture of about 40 to about 60% by weight of an immunoglobulin composition comprising

40

5 concentrated immunologically active immunoglobulins and about 40 to about 60% by weight of soluble dietary fiber selected from the group consisting of inulin, fructo-oligosaccharides, pectin, guar gum, and mixtures thereof.

10 It is also preferable that the formulation contain a beneficial human intestinal microorganism for restoring and maintaining good gastrointestinal health. The beneficial human intestinal microorganism is preferably a member selected from the group consisting of lactobacilli and bifidobacteria. Preferred lactobacilli include *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. fermentum*, *L. salivaroae*, *L. brevis*, *L. leichmannii*, *L. plantarum*, and *L. cellobiosus*. *L. acidophilus* is more preferred and *L. acidophilus* strain NCFM is most preferred. Preferred bifidobacteria include *B. adolescentis*, *B. infantis*, *B. longum*, *B. thermophilum*, and *B. bifidum*. *B. adolescentis* is more preferred. Such beneficial human intestinal bacteria can be added to the base formulation in an amount in the range of about 0 to about 20% by weight, preferably about 0.1 to about 20% by weight, and more preferably about 5 to about 10% by weight.

15 It is also preferable that the formulation contain one or more additives for enhancing the activity of the body's non-immune defense system known as the LP system. Such additives can be added to the base formulation, with or without the presence of optional ingredients, in the following concentrations: lactoperoxidase in an amount in the range of about 0 to about 0.0300% by weight and thiocyanate salt in an amount in the range of about 0 to about 0.0500% by weight. Preferably, lactoperoxidase is present in an amount in the range of about 0.0001 to about 0.0300% by weight, and thiocyanate salt is present in an amount in the range of about 0.0001 to about 0.0500% by weight.

5 It is also preferable that the formulation contain
additional optional ingredients for inhibiting the
growth of harmful intestinal microorganisms and/or
promoting the growth of beneficial human intestinal
microorganisms, such as bifidobacteria. Such additives
10 can be added to the base formulation, with or without
the presence of other optional ingredients, in the
following concentrations: lactoferrin in an amount in
the range of about 0 to about 0.1000% by weight and
gluconic acid, its nutritionally acceptable salts, or
mixtures thereof in an amount in the range of about 0 to
15 about 10% by weight. Preferably, lactoferrin is present
in an amount in the range of about 0.0001 to about
0.1000% by weight, and gluconic acid, its nutritionally
acceptable salts, or mixtures thereof in an amount in
20 the range of about 0.1 to about 10% by weight.

25 The composition is preferably manufactured in
powder form by agglomerating the dry, raw material
ingredients in a suitable agglomerator so as to result
in a finished product having a uniform composition with
the precise proportions of the components. The bacteria
are prepared, for example, by culturing in a rich medium
such as LB, J. Miller, Experiments in Molecular
Genetics, Cold Spring Harbor Laboratory, Cold Spring
Harbor, N.Y. (1972), until the late log phase of growth
30 is reached. The bacteria are then concentrated and
lyophilized according to standard methods. The
agglomerated material is then packaged in a suitable
container. Just prior to consumption, the dry
composition is reconstituted with water, juice, or the
35 like to result in a smooth liquid composition that can
be consumed orally. If desired, the composition can be
formulated in liquid form. The preferred daily dosage
of the formula ranges from about 5 to about 15 grams
based on the powdered composition. The daily dosage can
40 be ingested in a single serving or divided into various
servings and taken at intervals. Preferably, the

5 composition of the present invention is taken between meals.

The composition of the present invention can be used for maintaining gastrointestinal health as well as for treating diarrhea, constipation, and other types of 10 gastrointestinal distress due to infection with pathogenic microorganisms such as *E. coli*, *Salmonella*, *Candida*, rotavirus, and *Cryptosporidium* by orally administering an effective amount of the composition. The effective amount will vary depending on the size and 15 age of the individual, whether the selected effect is to maintain gastrointestinal health or to restore gastrointestinal health from distress due to infection with a pathogenic microorganism, the particular pathogenic microorganism involved, and the like. A 20 person skilled in the art can routinely determine such an effective amount. The dry ingredients of the composition are stirred into water or juice, and the resulting suspension is taken by mouth. Preferably, dosage is in the range of about 20 to about 400 mg/kg of 25 body weight. More preferably, dosage is in the range of about 70 to about 215 mg/kg of body weight. Doses of the bacteria and immunoglobulin-containing composition can be divided, wherein two or more administrations of 30 divided doses are used to deliver a complete dose. Multiple doses can also be administered, but it is recommended that daily consumption be limited to 1 to 3 doses.

EXAMPLE 12

35 The following formulas represent specific embodiments of the invention. These may be prepared in the manner indicated above by blending together the stated raw ingredients in an agglomerator so as to result in a finished product having uniform composition with the precise proportions of the components as indicated. The agglomerated material is then packaged 40 in a suitable container. In the preferred embodiment,

5 the formula comprises the following ingredients stated
in amounts by weight:

Formulation A

	Inulin	50%
	Immunoglobulin comp.	50%

10 Formulation B

	Inulin	40%
	Immunoglobulin comp.	40%
15	<i>L. acidophilus</i> NCFM	20%

Formulation C

	Pectin	40%
20	Immunoglobulin comp.	60%

Formulation D

	Guar Gum	20%
25	Pectin	30%
	Immunoglobulin comp.	40%
	<i>B. adolescentis</i>	10%

Formulation E

	Inulin	30%
	FOS	15%
30	Immunoglobulin comp.	49.72%
	<i>L. acidophilus</i> NCFM	2.5%
35	<i>B. adolescentis</i>	2.5%
	Lactoperoxidase	0.03%
	Sodium thiocyanate	0.05%
	Lactoferrin	0.1%
40	Gluconic acid	0.1%

Formulation F

	Inulin	40%
45	Pectin	9.98%
	Immunoglobulin comp.	40%
	<i>B. adolescentis</i>	10%
	Lactoperoxidase	0.02%

5 Formulation G

	Inulin	10%
	FOS	10%
	Pectin	10%
10	Guar Gum	10%
	Immunoglobulin comp.	52.95%
	<i>L. acidophilus NCFM</i>	7%
	Potassium thiocyanate	0.05%

15 Formulation H

	Inulin	50.9%
	Immunoglobulin comp.	40%
20	<i>B. adolescentis</i>	9%
	Lactoferrin	0.1%

Formulation I

25	Inulin	42%
	Immunoglobulin comp.	40%
	<i>B. adolescentis</i>	8%
	Sodium gluconate	10%

Formulation J

30	Inulin	20%
	FOS	20%
	Pectin	4.44%
	Guar Gum	1%
35	Immunoglobulin comp.	40%
	<i>B. adolescentis</i>	10%
	Lactoperoxidase	0.01%
	Ammonium thiocyanate	0.05%
	Sodium gluconate	4.5%

40 Formulation K

45	FOS	36%
	Pectin	3.5%
	Guar Gum	2.5%
	Immunoglobulin comp.	42%
	<i>L. acidophilus NCFM</i>	10%
	Lactoferrin	0.01%
	Gluconic acid	5.99%

50 Formulation L

55	Inulin	40%
	Immunoglobulin comp.	40%
	<i>B. adolescentis</i>	10%
	Lactoperoxidase	0.0001%
	Sodium thiocyanate	0.0001%
	Lactoferrin	0.0001%
	Gluconic acid	10%

5

Claims

I claim:

1. An immunoglobulin and fiber-containing composition comprising in percent by weight

10 (a) about 40 to about 60% of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins; and

15 (b) about 40 to about 60% of soluble dietary fiber, wherein said fiber is a member selected from the group consisting of inulin, fructo-oligosaccharides, pectin, guar gum, and mixtures thereof.

2. The composition of claim 1 further comprising about 0.1 to about 20% by weight of a beneficial human intestinal microorganism selected from the group consisting of lactobacilli and bifidobacteria.

20 3. The composition of claim 1 further comprising about 0.0001% to 0.0500% by weight of thiocyanate salt and about 0 to about 0.0300% by weight of lactoperoxidase.

30 4. The composition of claim 2 further comprising about 0.0001% to about 0.0500% by weight of thiocyanate salt and about 0 to about 0.0300% by weight of lactoperoxidase.

5. The composition of claim 4 comprising about 0.0001% to about 0.0300% by weight of lactoperoxidase.

35 6. The composition of claim 1 further comprising about 0.0001% to about 0.1000% of lactoferrin and about 0 to about 10% by weight of a member selected from the group consisting of gluconic acid, its nutritionally acceptable salts, and mixtures thereof.

5 7. The composition of claim 2 further comprising about 0.0001% to about 0.1000% of lactoferrin and about 0 to about 10% by weight of a member selected from the group consisting of gluconic acid, its nutritionally acceptable salts, and mixtures thereof.

10

10 8. The composition of claim 3 further comprising about 0.0001% to about 0.1000% of lactoferrin and about 0 to about 10% by weight of a member selected from the group consisting of gluconic acid, its nutritionally acceptable salts, and mixtures thereof.

15

20 9. The composition of claim 4 further comprising about 0.0001% to about 0.1000% of lactoferrin and about 0 to about 10% by weight of a member selected from the group consisting of gluconic acid, its nutritionally acceptable salts, and mixtures thereof.

25

25 10. The composition of claim 9 comprising about 0.1% to about 10% by weight of a member selected from the group consisting of gluconic acid, its nutritionally acceptable salts, and mixtures thereof.

30

11. The composition of claim 2 wherein said beneficial human intestinal microorganism is a member selected from the group consisting of *Lactobacillus acidophilus*, *L. bulgaricus*, *L. casei*, *L. fermentum*, *L. salivaroer*, *L. brevis*, *L. leichmannii*, *L. plantarum*, and *L. cellobiosus*.

35

12. The composition of claim 11 wherein said beneficial human intestinal microorganism is *Lactobacillus acidophilus*.

40

13. The composition of claim 12 wherein said *Lactobacillus acidophilus* is strain NCFM.

5 14. The composition of claim 2 wherein said beneficial human intestinal microorganism is a member selected from the group consisting of *Bifidobacterium adolescentis*, *B. infantis*, *B. longum*, *B. thermophilum*, and *B. bifidum*.

10 15. The composition of claim 14 wherein said beneficial human intestinal microorganism is *B. adolescentis*.

15 16. The composition of claim 1 wherein said immunoglobulin composition further comprises a carrier.

20 17. The composition of claim 16 wherein said carrier comprises at least one member selected from the group consisting of a carbohydrate and a lipid, wherein said carbohydrate is capable of being an energy source for a beneficial human intestinal microorganism and said lipid aids in reconstitution of said immunoglobulin composition.

25 18. The composition of claim 17 wherein said carbohydrate comprises maltodextrin and said lipid comprises lecithin.

30 19. The composition of claim 1 wherein said immunoglobulin composition is purified from a source selected from the group consisting of milk, milk products, and whey.

35 20. The composition of claim 19 wherein said source is bovine.

40 21. A bacteria and immunoglobulin-containing composition for promoting gastrointestinal health comprising

- 5 (a) an effective amount of a beneficial human intestinal microorganism; and
 (b) an effective amount of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins.

10

22. The composition of claim 21 wherein said beneficial human intestinal microorganism is selected from the group consisting of lactobacilli and bifidobacteria.

15

23. The composition of claim 22 wherein the weight ratio of beneficial human intestinal microorganism to immunologically active immunoglobulins is in the range of about 20:1 to about 1:20.

20

24. The composition of claim 23 wherein weight ratio of beneficial human intestinal microorganism to immunologically active immunoglobulins is in the range of about 1:5 to about 10:1.

25

25. The composition of claim 24 wherein said beneficial human intestinal microorganism is a lactobacillus.

30

26. The composition of claim 25 wherein said lactobacillus is selected from the group consisting of *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. fermentum*, *L. salivaroës*, *L. brevis*, *L. leichmannii*, *L. plantarum*, and *L. cellobiosus*.

35

27. The composition of claim 26 wherein said lactobacillus is *Lactobacillus acidophilus*.

40

28. The composition of claim 27 wherein said *Lactobacillus acidophilus* is strain NCFM.

5 29. The composition of claim 24 wherein said
beneficial human intestinal microorganism is a
bifidobacterium.

10 30. The composition of claim 29 wherein said
bifidobacterium is selected from the group consisting of
Bifidobacterium adolescentis, *B. infantis*, *B. longum*, *B.*
thermophilum, and *B. bifidum*.

15 31. The composition of claim 30 wherein said
bifidobacterium is *B. adolescentis*.

32. The composition of claim 21 wherein said
immunoglobulin composition further comprises a carrier.

20 33. The composition of claim 32 wherein said
carrier comprises at least one member selected from the
group consisting of a carbohydrate and a lipid, wherein
said carbohydrate is capable of being an energy source
for said beneficial human intestinal microorganism and
said lipid aids in reconstitution of said immunoglobulin
composition.

30 34. The composition of claim 35 wherein said
carbohydrate comprises maltodextrin and said lipid
comprises lecithin.

35 35. The composition of claim 21 wherein said
immunoglobulin composition is purified from a source
selected from the group consisting of milk, milk
products, and whey.

36. The composition of claim 35 wherein said
source is bovine.

40 37. A method of restoring and maintaining
gastrointestinal health comprising the step of orally

5 administering a bacteria and immunoglobulin-containing
composition comprising an effective amount of a
beneficial human intestinal microorganism and an
effective amount of an immunoglobulin composition
comprising concentrated immunologically active
10 immunoglobulins.

15 38. The method of claim 37 wherein said beneficial
human intestinal microorganism is a member selected from
the group consisting of lactobacilli and bifidobacteria.

20 39. The method of claim 38 wherein the weight
ratio of beneficial human intestinal microorganism to
immunologically active immunoglobulins is in the range
of about 20:1 to about 1:20.

25 40. The method of claim 39 wherein the weight
ratio of beneficial human intestinal microorganism to
immunologically active immunoglobulins is in the range
of about 1:5 to about 10:1.

30 41. The method of claim 40 wherein said
lactobacilli are selected from the group consisting of
L. acidophilus, *L. bulgaricus*, *L. casei*, *L. fermentum*,
L. salivaroës, *L. brevis*, *L. leichmannii*, *L. plantarum*,
and *L. cellobiosus* and said bifidobacteria are selected
from the group consisting of *Bifidobacterium
adolescentis*, *B. infantis*, *B. longum*, *B. thermophilum*,
and *B. bifidum*.

35 42. The method of claim 41 wherein said beneficial
human intestinal microorganism is *Lactobacillus
acidophilus*.

40 43. The method of claim 41 wherein said beneficial
human intestinal microorganism is *B. adolescentis*.

5 44. The method of claim 41 wherein said immunoglobulin composition is purified from a source selected from the group consisting of bovine milk, milk products, and whey.

10 45. A method of restoring and maintaining gastrointestinal health comprising the step of orally administering an effective amount of an immunoglobulin and fiber-containing composition for promoting gastrointestinal health comprising in percent by weight

15 (a) about 40 to about 60% of an immunoglobulin composition comprising concentrated immunologically active immunoglobulins; and

20 (b) about 40 to about 60% of soluble dietary fiber, wherein said fiber is a member selected from the group consisting of inulin, fructo-oligosaccharides, pectin, guar gum, and mixtures thereof.

25 46. The method of claim 45 wherein said immunoglobulin and fiber-containing composition further comprises about 0.1 to about 20% by weight of a beneficial human intestinal microorganism selected from the group consisting of lactobacilli and bifidobacteria.

30 47. The method of claim 46 wherein said lactobacilli are selected from the group consisting of *Lactobacillus acidophilus*, *L. bulgaricus*, *L. casei*, *L. fermentum*, *L. salivaroer*, *L. brevis*, *L. leichmannii*, *L. plantarum*, and *L. cellobiosus* and said bifidobacteria are selected from the group consisting of *Bifidobacterium adolescentis*, *B. infantis*, *B. longum*, *B. thermophilum*, and *B. bifidum*.

40 48. The method of claim 47 wherein said beneficial human intestinal microorganism is *Lactobacillus acidophilus*.

5 49. The method of claim 47 wherein said beneficial
human intestinal microorganism is *B. adolescentis*.

10 50. The method of claim 45 wherein said
immunoglobulin and fiber-containing composition further
comprises about 0.0001% to 0.0500% by weight of
thiocyanate salt and about 0 to about 0.0300% by weight
of lactoperoxidase.

15 51. The method of claim 45 wherein said
immunoglobulin and fiber-containing composition further
comprises about 0.0001% to about 0.1000% of lactoferrin
and about 0 to about 10% by weight of a member selected
from the group consisting of gluconic acid, its
nutritionally acceptable salts, and mixtures thereof.

20 52. The method of claim 45 wherein said
immunoglobulin composition is purified from a source
selected from the group consisting of bovine milk, milk
products, and whey.

1/3

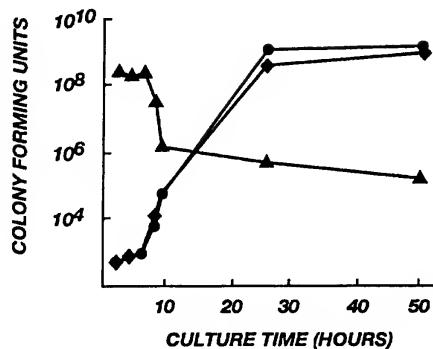


Fig. 1

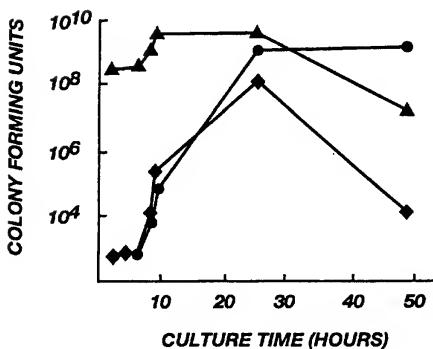


Fig. 2

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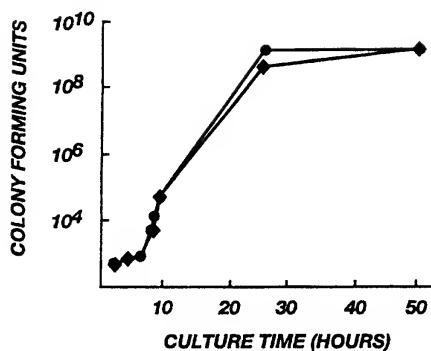


Fig. 3

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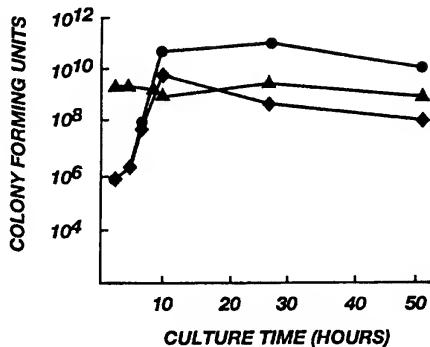


Fig. 4

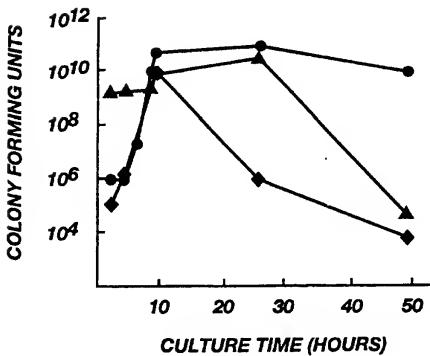


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No. PCT/US95/13905

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 35/00, 35/20, 39/02, 39/07, 39/395, 39/40, 39/42, 47/00
 US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,816,252 (STOTT ET AL.) 28 MARCH 1989, see entire document.	1-52
A	US, A, 4,977,137 (NICHOLS ET AL.) 11 DECEMBER 1990, see entire document.	1-52
A	US, A, 5,240,909 (NITSCHE) 31 AUGUST 1993, see entire document.	1-52
A	Journal of Food Protection, Volume 40, Number 12, issued December 1977, Gilliland et al., "Antagonistic Action of <i>lactobacillus acidophilus</i> Toward Intestinal and Foodborne Pathogens in Associative cultures", pages 820-823, see entire document.	1-52

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
25 JANUARY 1996	08 FEB 1996

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No. PCT/US95/13905

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Journal of Dairy Science, Volume 73, Number 4, issued 1990, Gilliland et al., "Factors to Consider When Selecting a Culture of <i>Lactobacillus Acidophilus</i> as a Dietary Adjunct to Produce a Hypocholesterolemic Effect in Humans", pages 905-911, see entire document.	1-52
A	Annals of Internal Medicine, Volume 116, Number 5, issued 01 March 1992, Hilton et al., "Ingestion of Yogurt Containing <i>Lactobacillus Acidophilus</i> as Prophylaxis for Candidal Vaginitis", pages 353-357, see entire document.	1-52
A	New England Journal of Medicine, Volume 318, Number 19, issued 12 May 1988, Tacket et al., "Protection by Milk Immunoglobulin Concentrate Against Oral Challenge With Enterotoxigenic <i>Escherichia Coli</i> ", pages 1240-1243, see entire document.	1-52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/13905

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/93.4, 93.45, 130.1, 143.1, 145.1, 147.1, 148.1, 149.1, 150.1, 151.1, 157.1, 158.1, 159.1, 161.1, 195.1, 234.1, 499, 500, 535, 809; 514/2, 439, 441, 445, 777, 867

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

424/93.4, 93.45, 130.1, 133.1, 135.1, 135.6, 141.1, 143.1, 145.1, 147.1, 148.1, 149.1, 150.1, 151.1, 157.1, 158.1, 159.1, 161.1, 195.1, 234.1, 499, 500, 535, 809; 514/2, 439, 441, 445, 484, 485, 777, 867